Misuse and Misapplication in Statistical Data Analysis

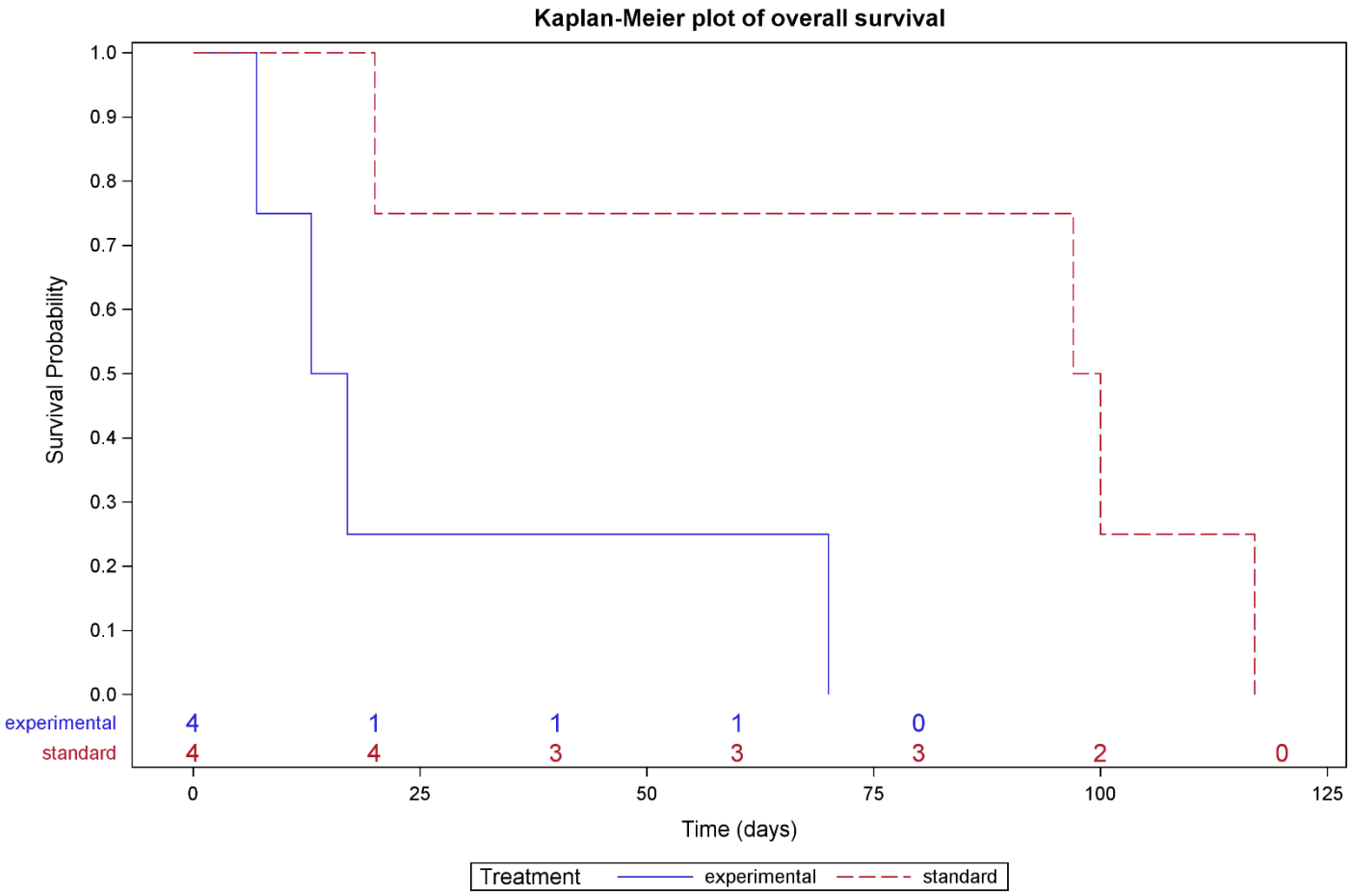
– A topic that never goes out of style

Corinna Miede

PhUSE SDE Basel

28-Jun-2018

Motivation



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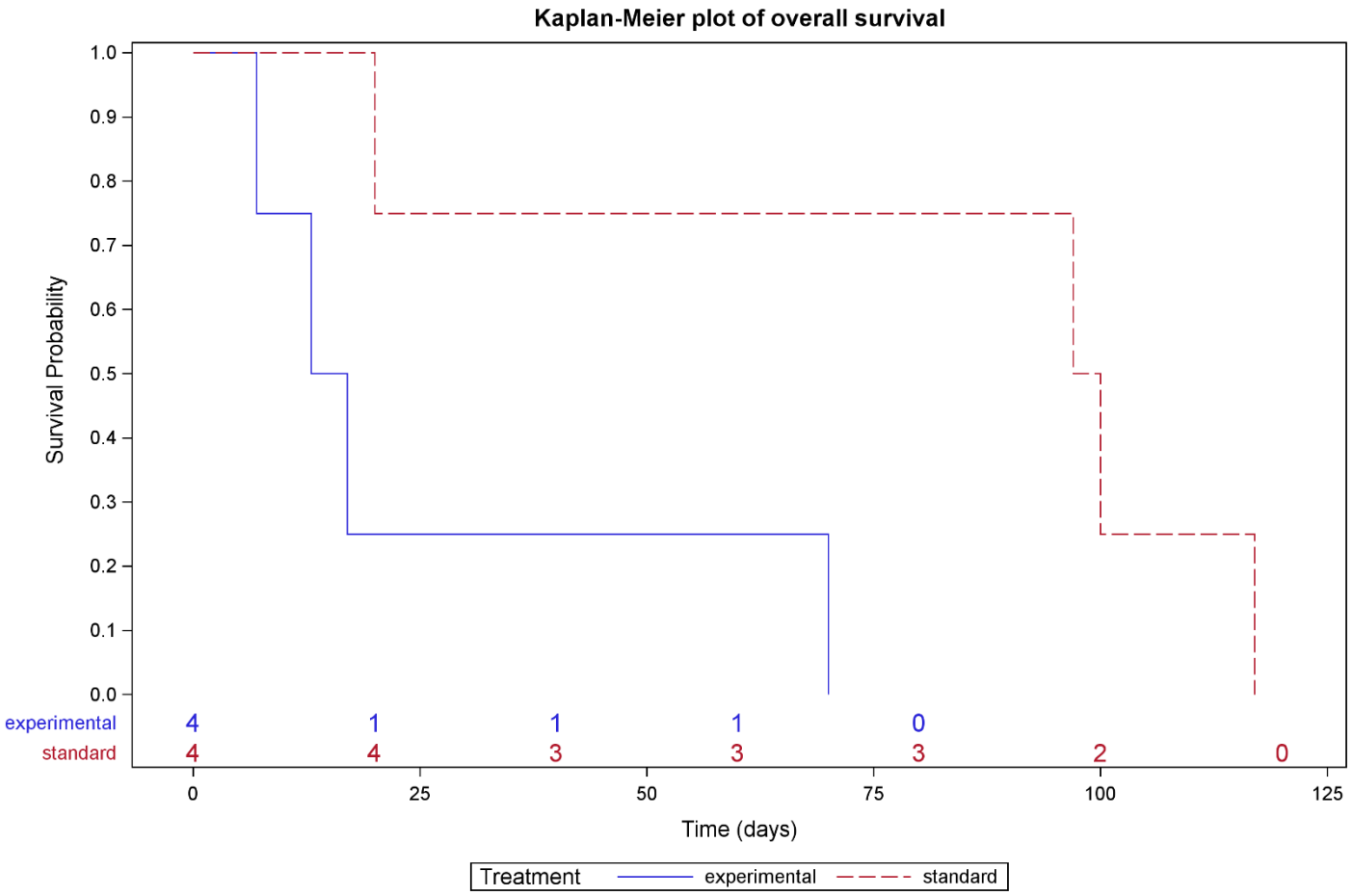
Motivation



- All patients died? 😱

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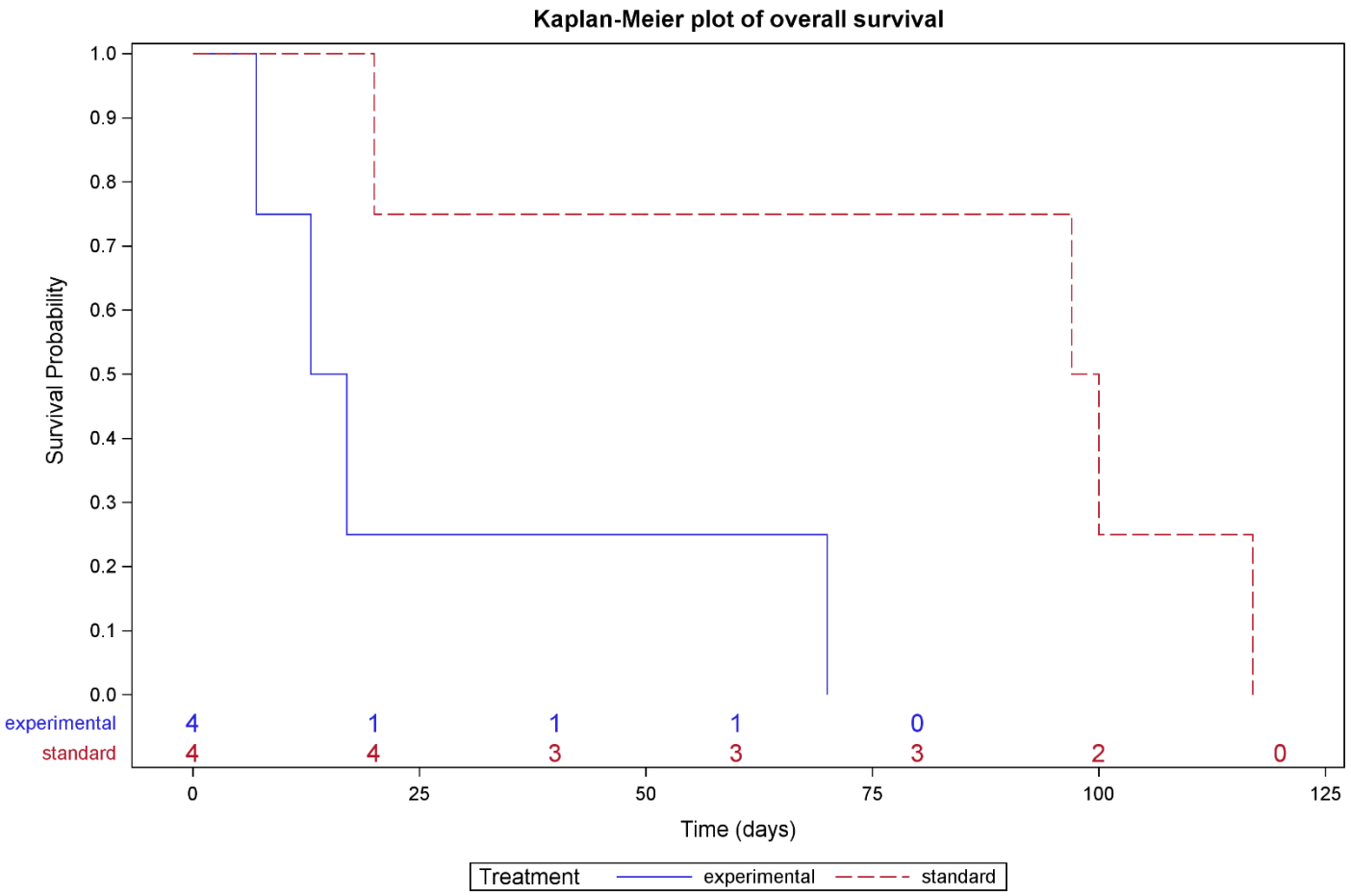
Motivation



- All patients died?
- Only 4 patients in each treatment group?

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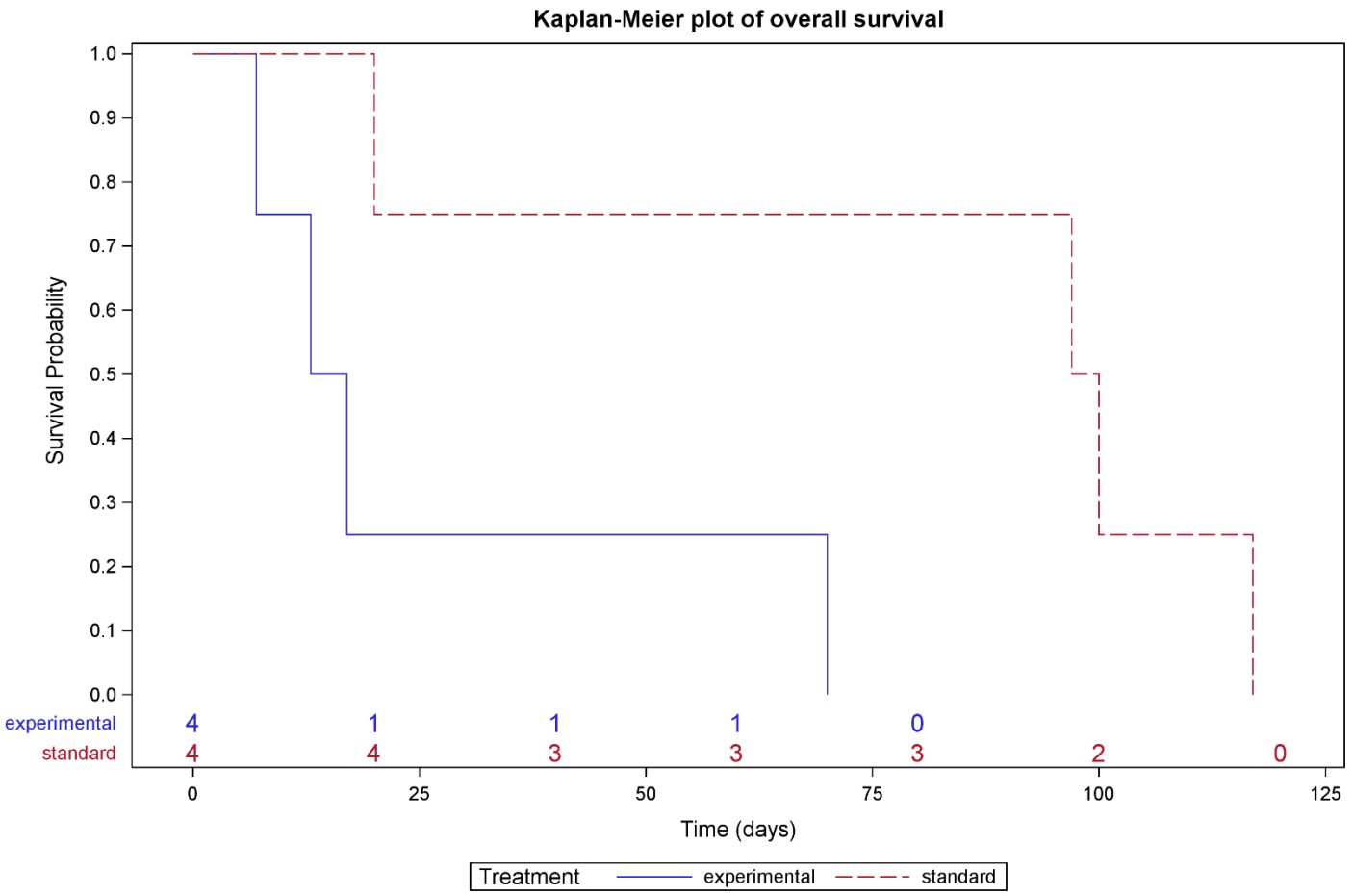
Motivation



- All patients died?
- Only 4 patients in each treatment group?
- Only patients with events are included!

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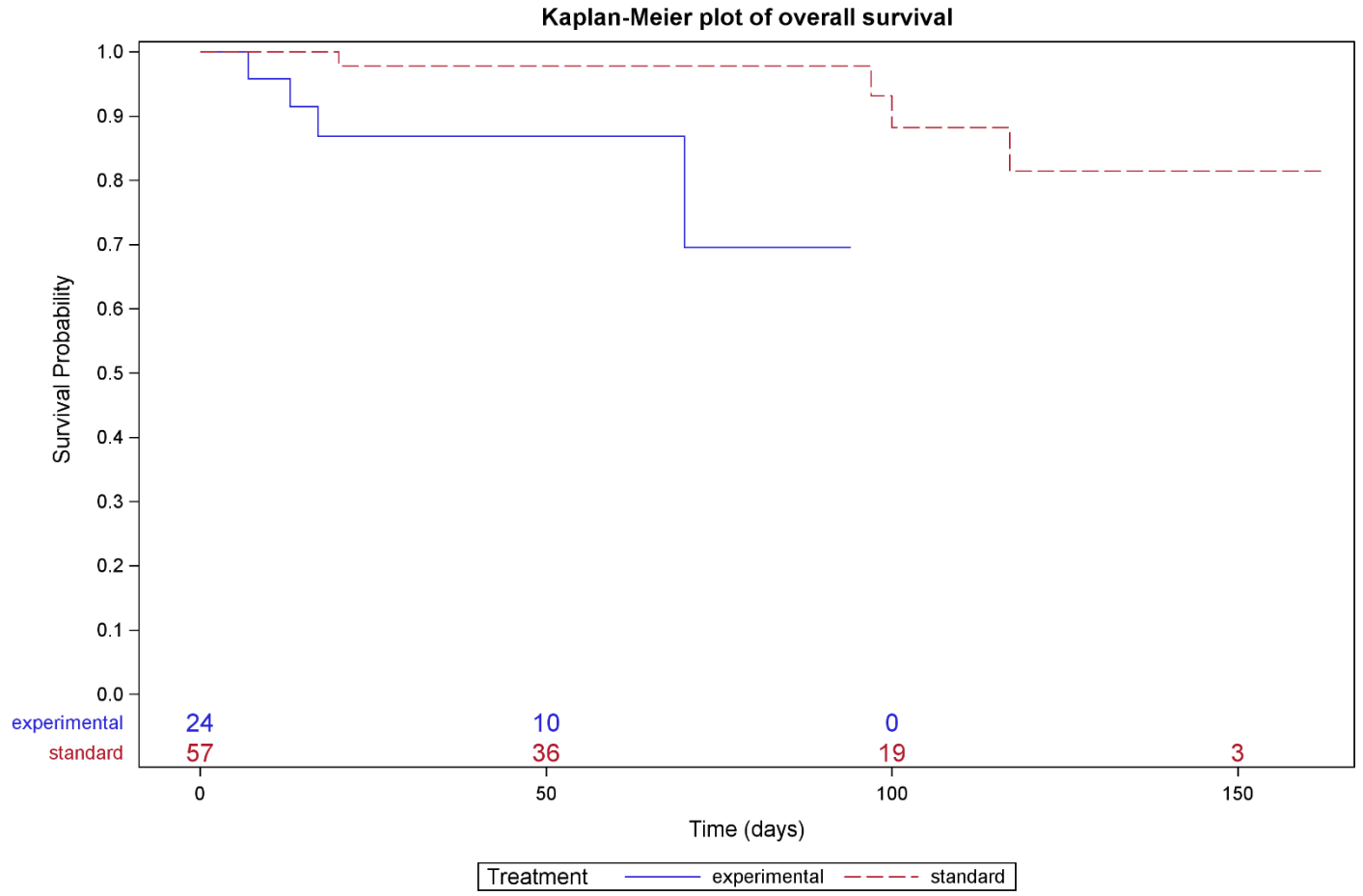
Motivation

Correct KM-plot



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Motivation

Challenger disaster

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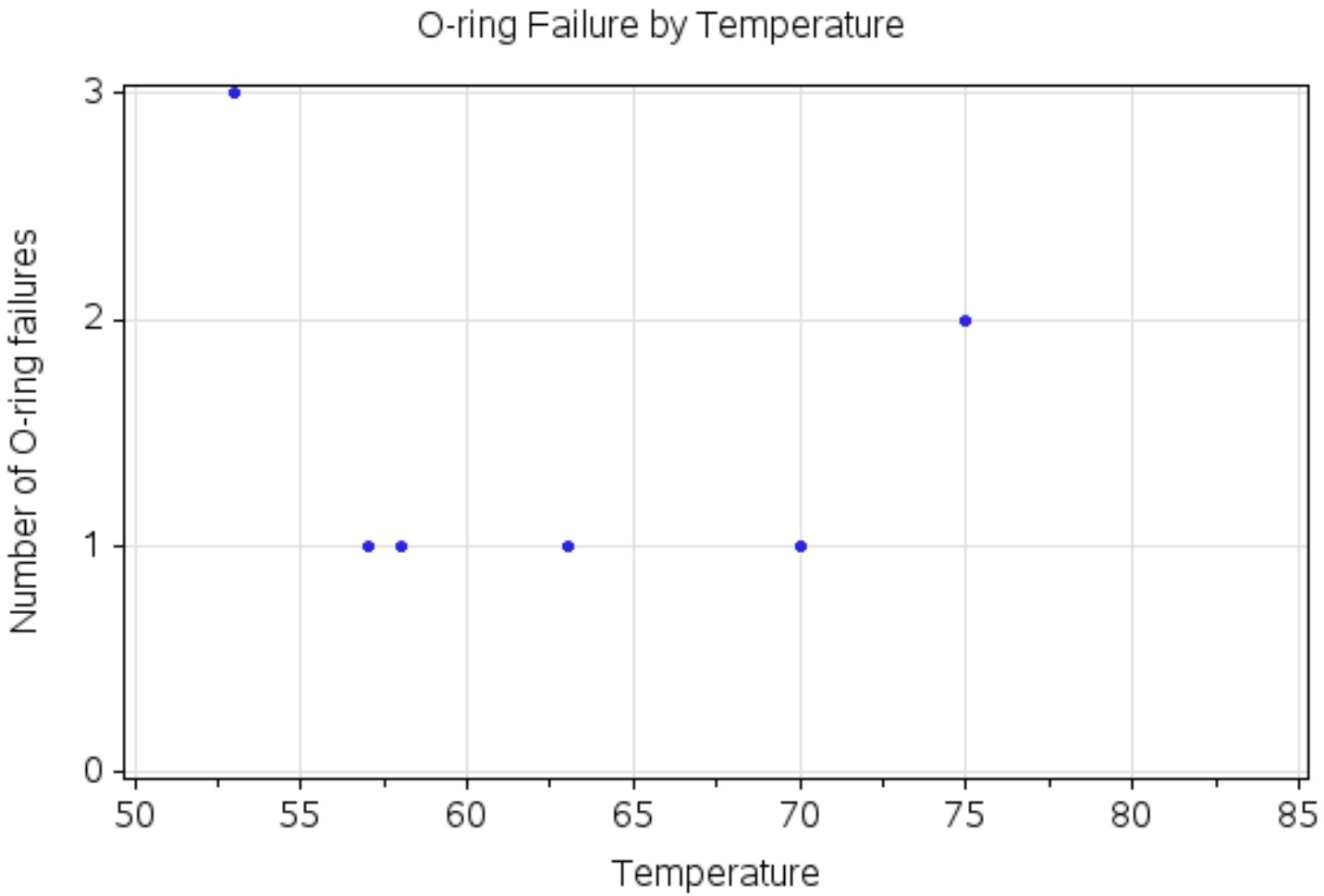
Motivation

Challenger disaster



- Data analyzed before space shuttle start
- Flights with incidents of O-rings
- No relationship between temperature and failure was detected
- Thus, decision for shuttle launch

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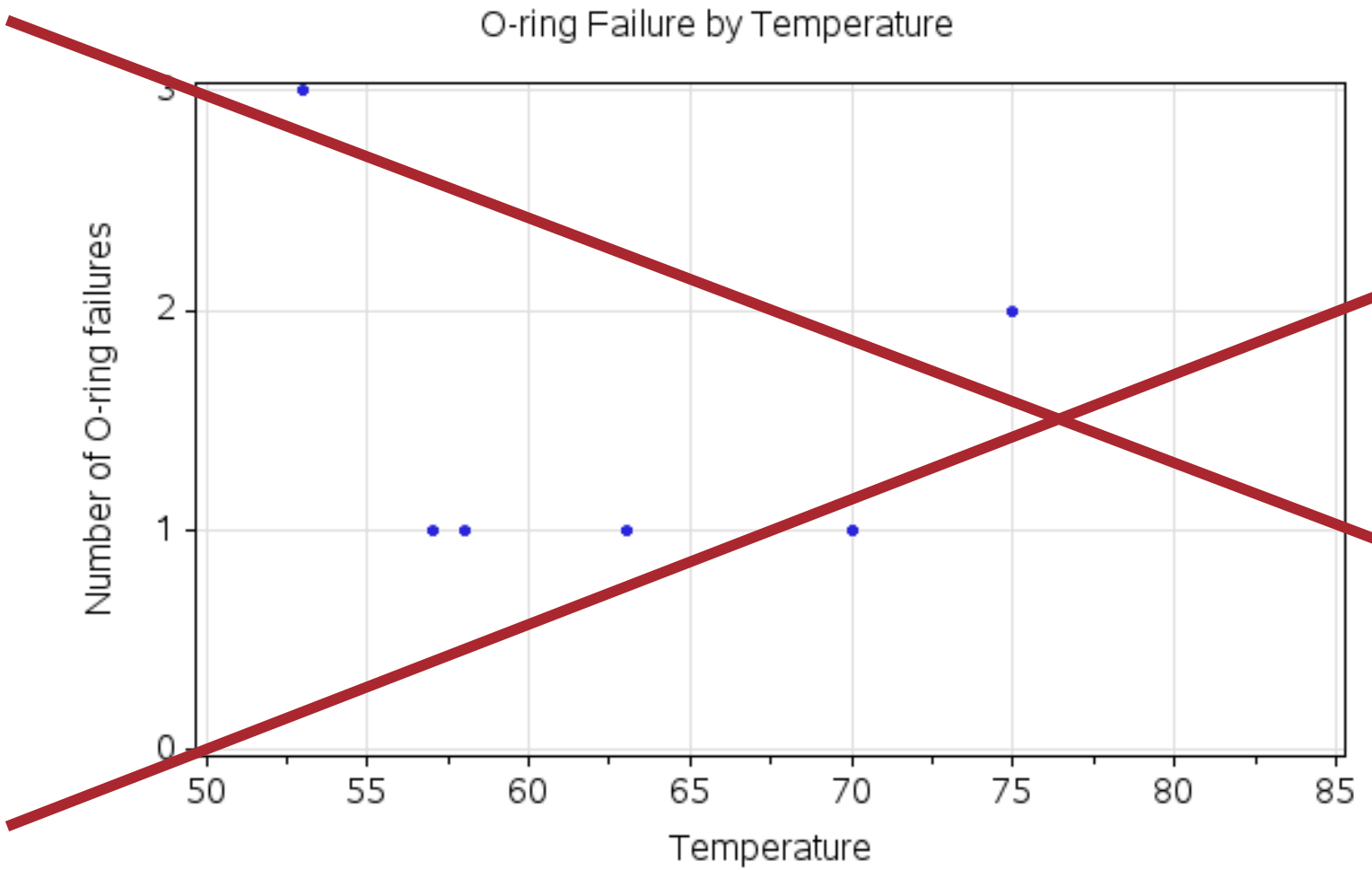
Motivation

Challenger disaster: wrong visualization



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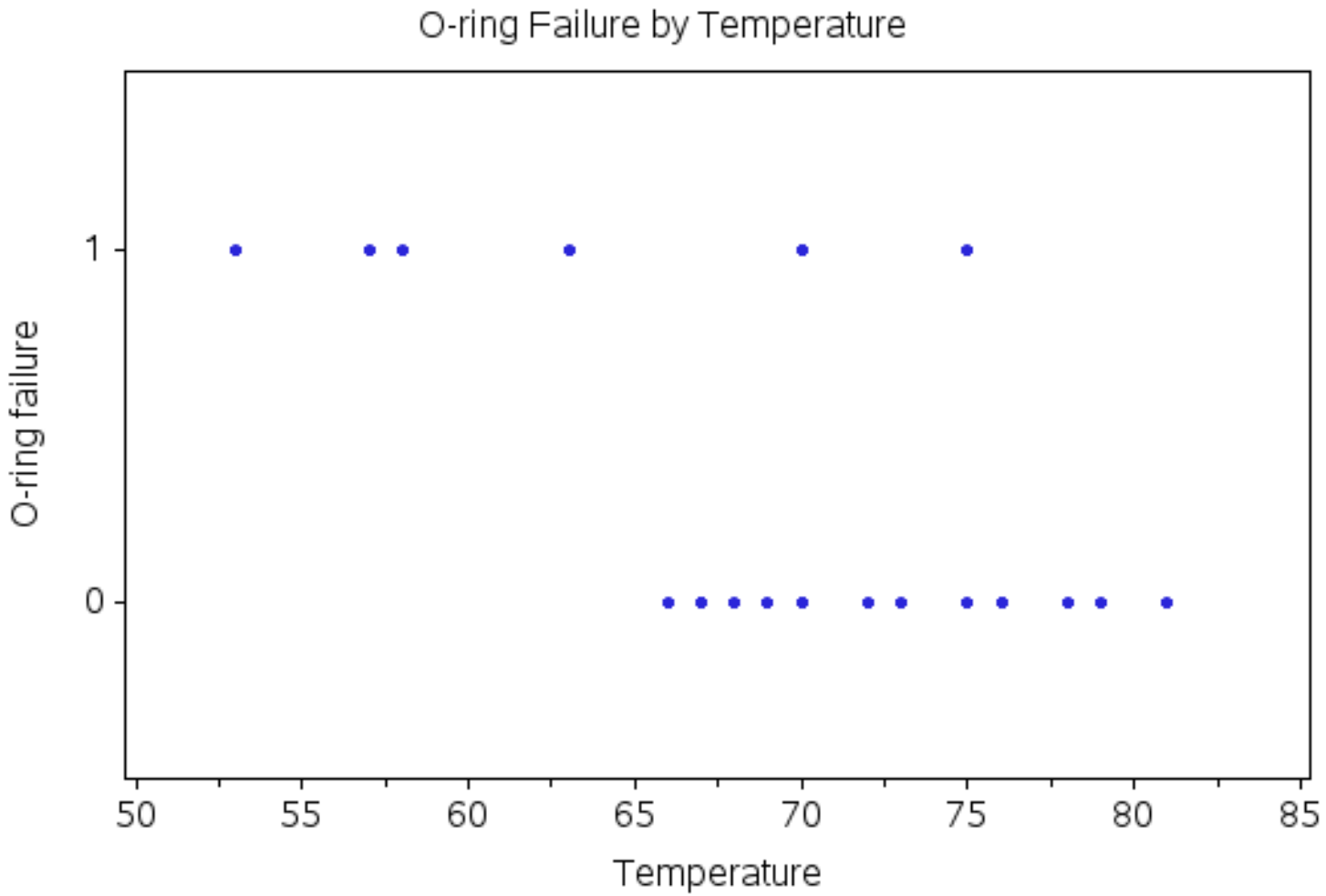
Motivation

Challenger disaster



- Include flights without any incidents of O-ring failure
- Relationship between temperature and failure is visible
- Temperature on the day of the launch was 31°F, so even colder than the minimum temperature in the plot
- They probably would have decided against shuttle launch

Introduction

Question: What this has to do with…

Future of Analytics?

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Introduction

Future Analytics

- Data visualization and new analytical tools are

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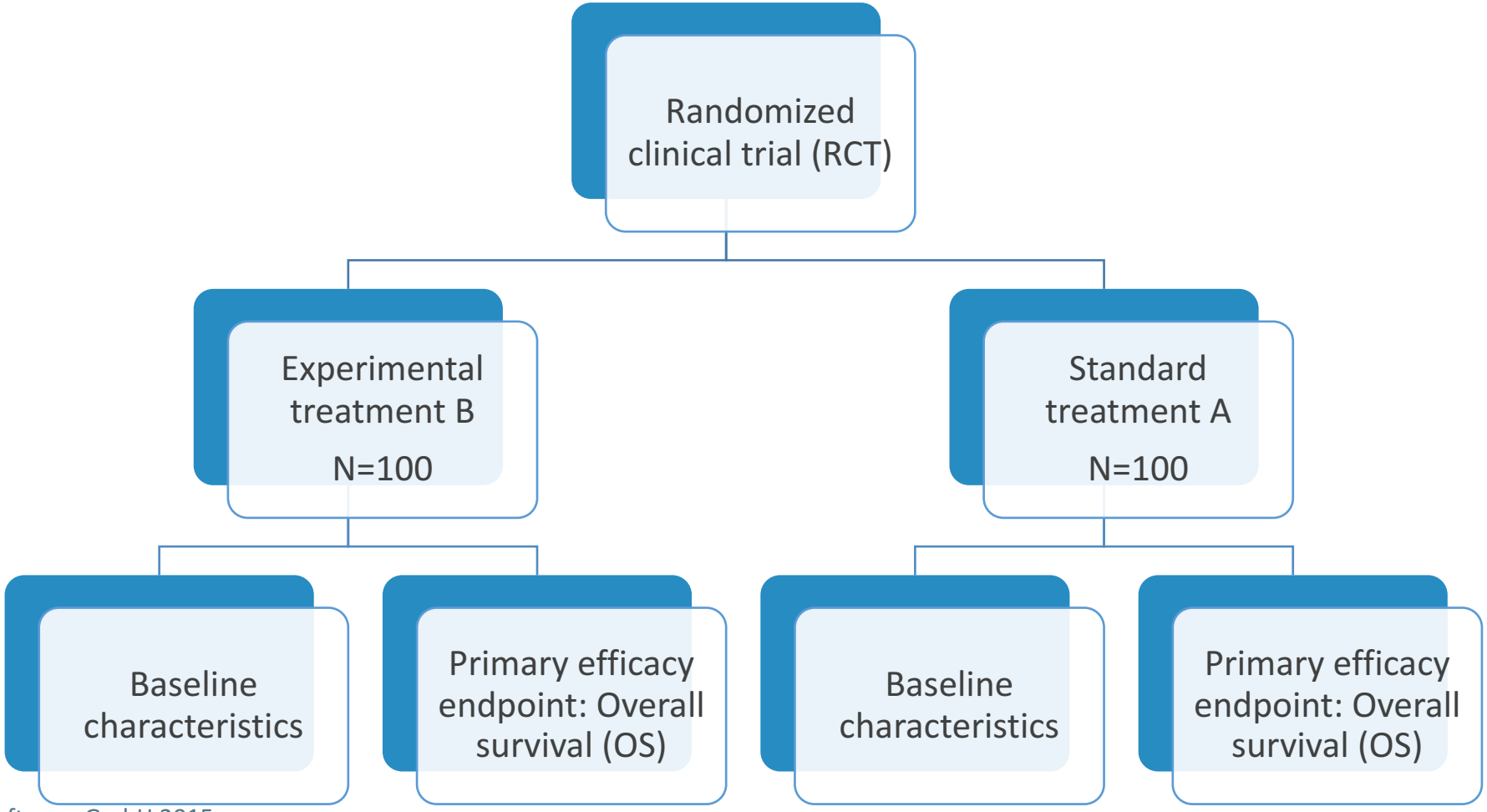
Introduction

Example Study



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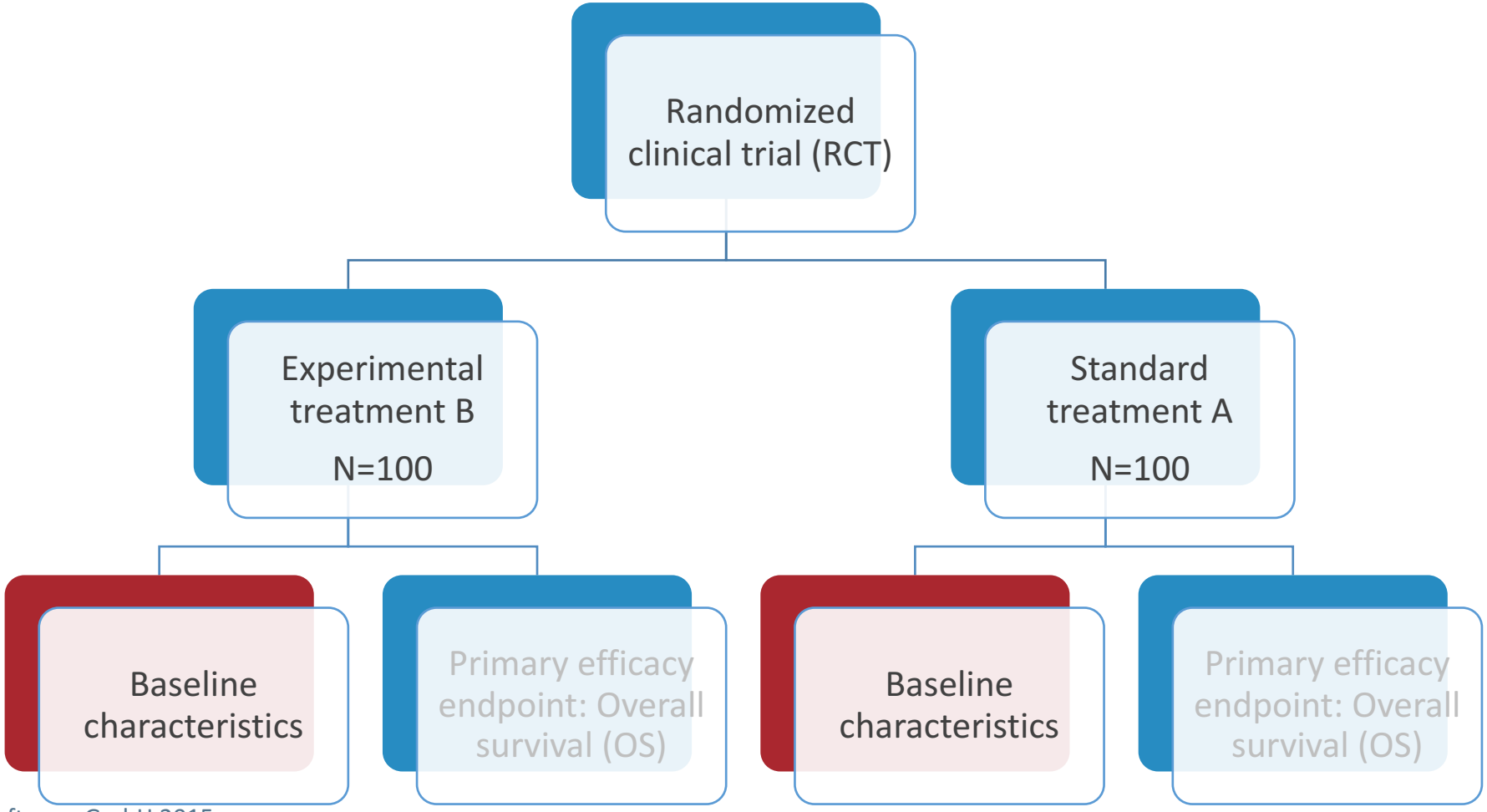
First Example

Baseline characteristics



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First Simple (Well-Known?) Example

Table of baseline characteristics

	Experimental treatment B	Standard treatment A
Number of patients, n (%)	100 (100)	100 (100)
Age		
Median (range)	62.0 (32-81)	60.5 (28-81)
Male sex, n (%)	71 (71.0)	72 (72.0)
…<other characteristics>	…	…
Bone marrow involvement, n (%)	23 (23.0)	28 (28.0)

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First Simple (Well-Known?) Example

Table of baseline characteristics

	Experimental treatment B	Standard treatment A
Number of patients, n (%)	100 (100)	100 (100)
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…<other characteristics>	…	…
Bone marrow involvement, n (%)	23 (23.0)	28 (28.0)

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First Simple (Well-Known?) Example

Table of baseline characteristics: Wrong conclusion

	Experimental treatment B	Standard treatment A
Number of patients, n (%)	100 (100)	100 (100)
Age		
Median (range)	62.0 (32-81)	60.5 (28-81)
Male sex, n (%)	71 (71.0)	72 (72.0)
…<other characteristics>	…	…
Bone marrow involvement, n (%)	23 (23.0)	28 (28.0)

- So, 77% and 72% without bone marrow involvement?
- Biopsy results from all patients available?
- What about missing data?

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First Simple (Well-Known?) Example

Table of baseline characteristics

	Experimental treatment B	Standard treatment A
Number of patients, n (%)	100 (100)	100 (100)
Age		
Median (range)	62.0 (32-81)	60.5 (28-81)
Male sex, n (%)	71 (71.0)	72 (72.0)
…<other characteristics>	…	…
Bone marrow involvement, n (%)	23 (23.0)	28 (28.0)

- So, 77% and 72% without bone marrow involvement?
- Biopsy results from all patients available?
- What about missing data?

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First Simple (Well-Known?) Example

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Table of baseline characteristics: Option 1

	Experimental treatment B	Standard treatment A
Number of patients, n (%)	100 (100)	100 (100)
Age		
Median (range)	62.0 (32-81)	60.5 (28-81)
Male sex, n (%)	71 (71.0)	72 (72.0)
…<other characteristics>	…	…
Bone marrow involvement, n (%)	23/82 (28.0)	28/83 (33.7)

- Percentages based on number of patients with non-missing data
- So, 18% and 17% of patients have missing data

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First Simple (Well-Known?) Example

Table of baseline characteristics: Option 2

	Experimental treatment B	Standard treatment A
Number of patients, n (%)	100 (100)	100 (100)
Age		
Median (range)	62.0 (32-81)	60.5 (28-81)
Male sex, n (%)	71 (71.0)	72 (72.0)
…<other characteristics>	…	…
Bone marrow involvement*, n (%)	23 (23.0)	28 (28.0)

* 18 (18.0%) and 17 (17.0%) patients with missing information

- Percentages based on total number of patients
- So, 59% and 55% of patients without bone marrow involvement

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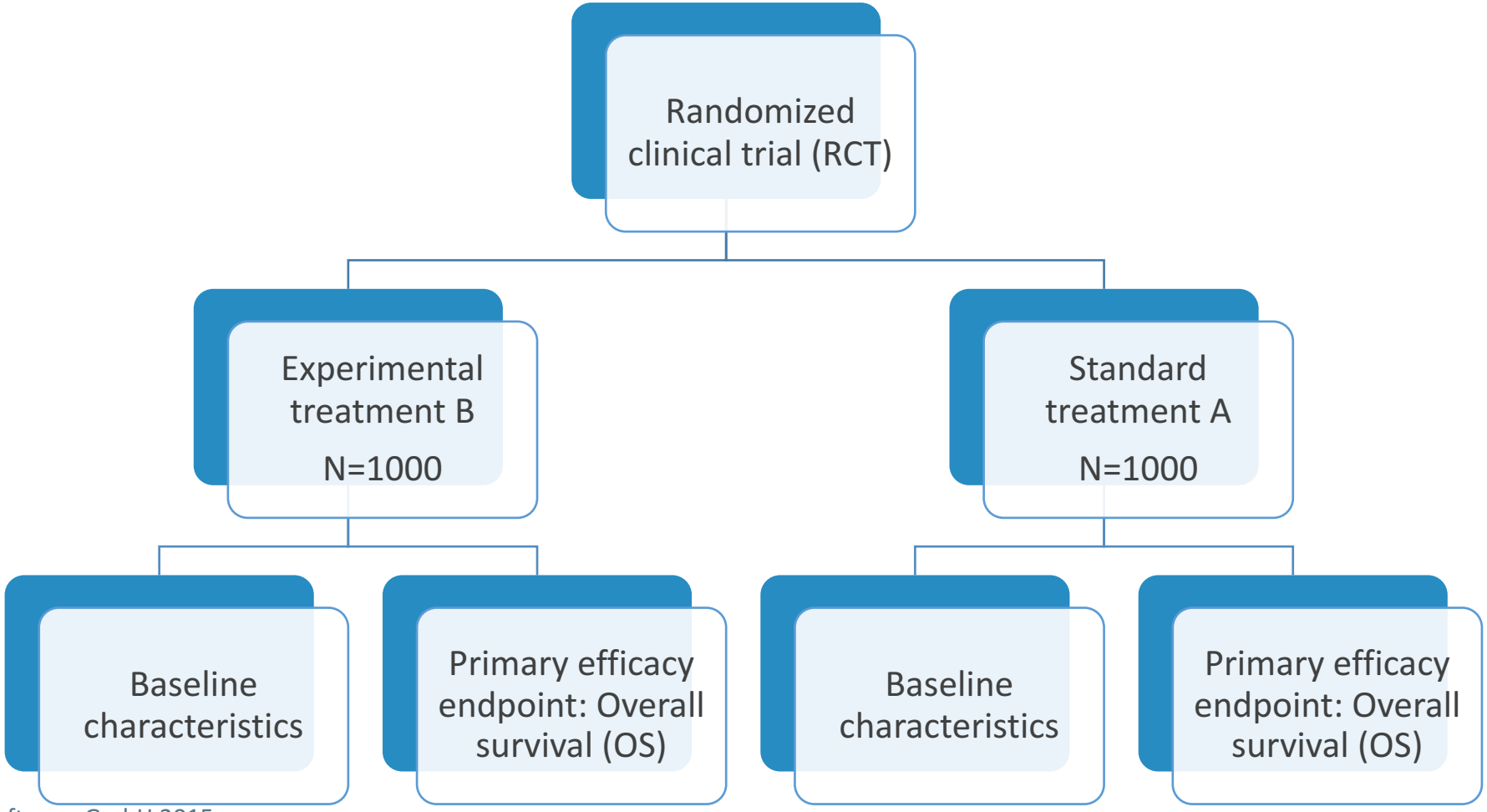
Example: Subgroup Analysis

Question: Same benefit within subgroups?



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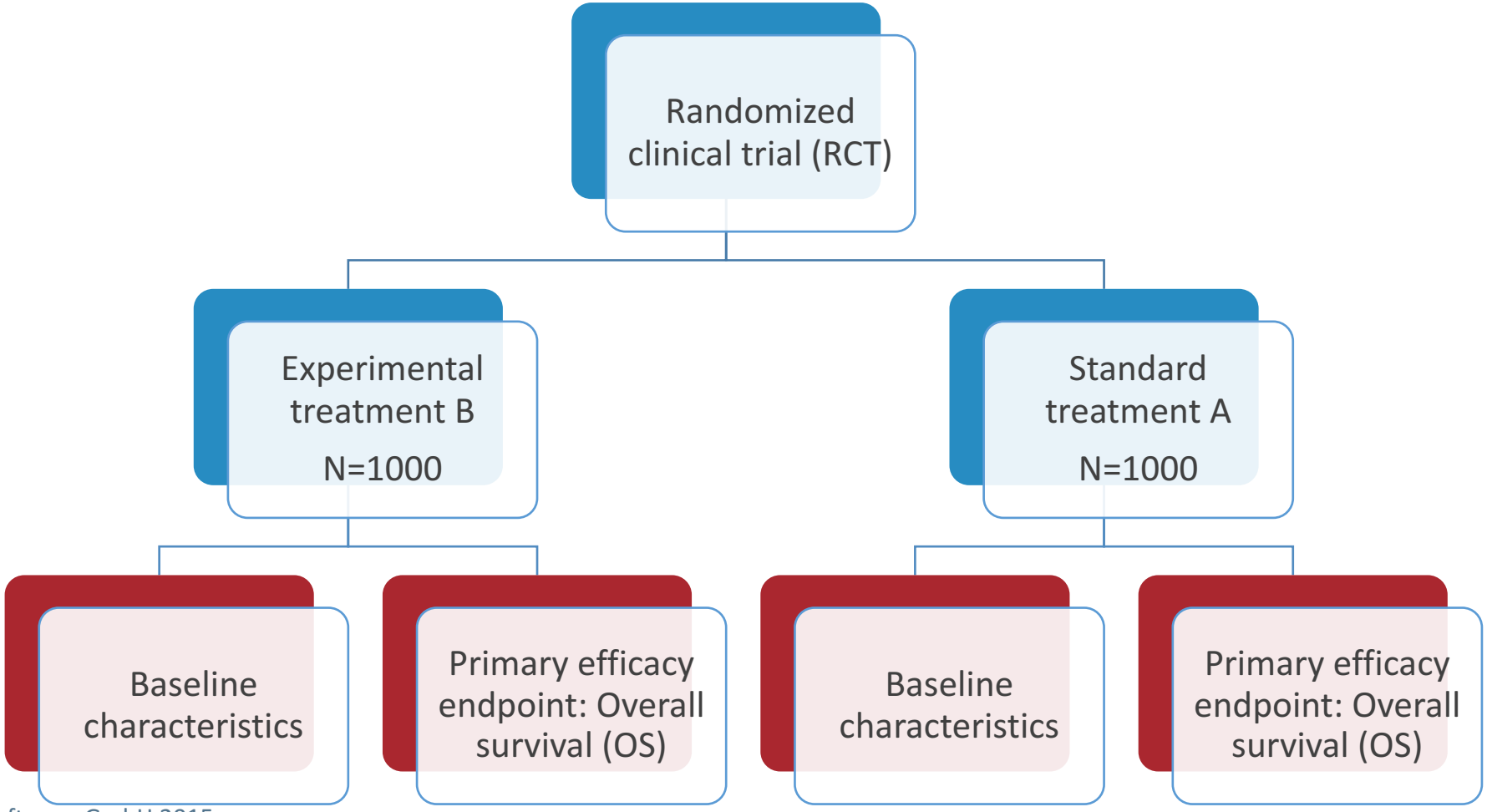
Example: Subgroup Analysis

Question: Same benefit within subgroups?



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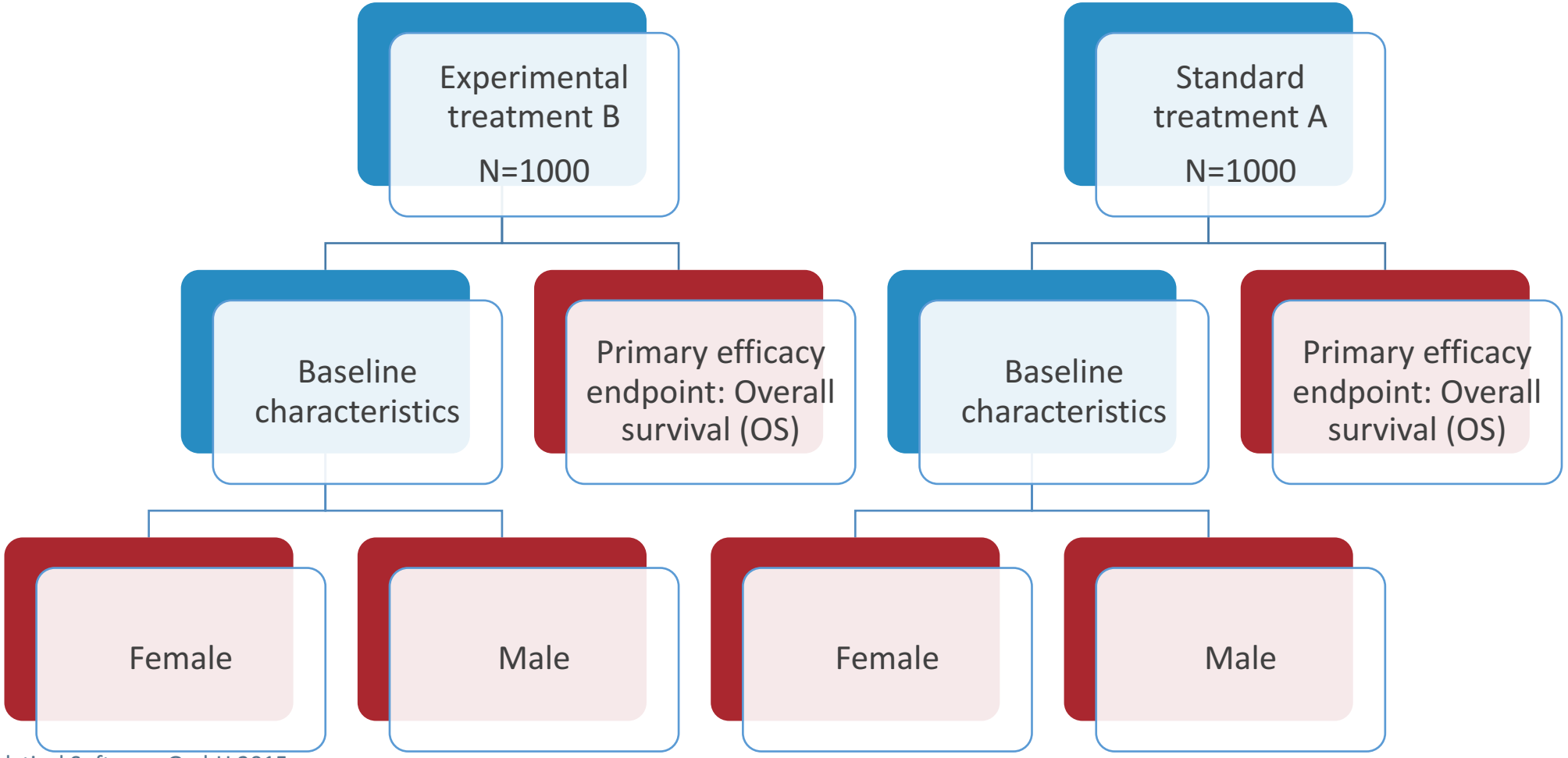
Example: Subgroup Analysis

Overall survival in female and male patients



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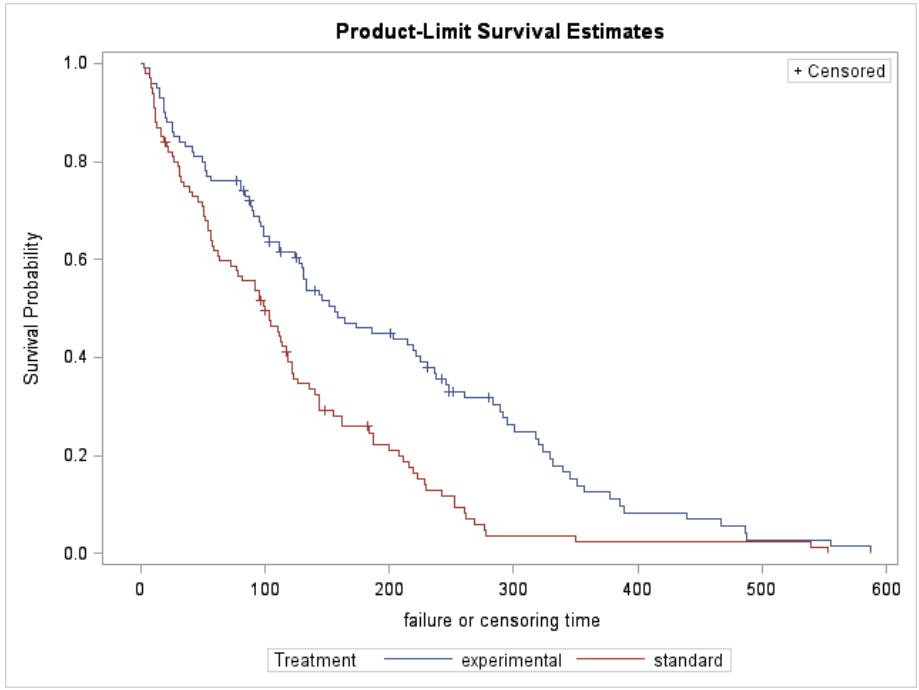
Example: Subgroup Analysis

Main results in overall population

	Experimental treatment B	Standard treatment A
Number of patients, n (%)	100 (100)	100 (100)
Overall survival		
Number of patients with events, n (%)	87 (87.0)	94 (94.0)
Hazard ratio* (95% CI)	0.54 (0.40, 0.73)	
p-value*	<0.0001	

* from Cox proportional hazard regression model



- Benefit of experimental treatment B over standard treatment A
- Is there a consistent benefit in male and female patients?

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Example: Subgroup Analysis

Overall survival in female and male patients

	Female		Male	
	Experimental treatment B	**Standard treatment A**	**Experimental treatment B**	**Standard treatment A**
Number of patients, n (%)	29 (100)	28 (100)	71 (100)	72 (100)
Overall survival				
Number of patients with events, n (%)	25 (86.2)	26 (92.9)	62 (87.3)	68 (94.4)
Hazard ratio* (95% CI)	0.64 (0.36, 1.13)		0.51 (0.36, 0.73)	
p-value*	0.1241		0.0003	

* from Cox proportional hazard regression model

- Benefit of experimental treatment B over standard treatment A only for male patients?

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Example: Subgroup Analysis

Limitations of subgroup analyses

- Sample size much lower within the single subgroup categories and often not balanced between the categories (e.g. female prevalence lower than male prevalence)
- Study powered only for the analysis of the primary endpoint in the overall population, not for any subgroup analysis (even if pre-specified)
- Multiplicity: higher probability of incorrectly rejecting at least one null hypothesis (i.e. higher probability of incorrectly detecting a significant difference)

→ Better approach: Interaction test

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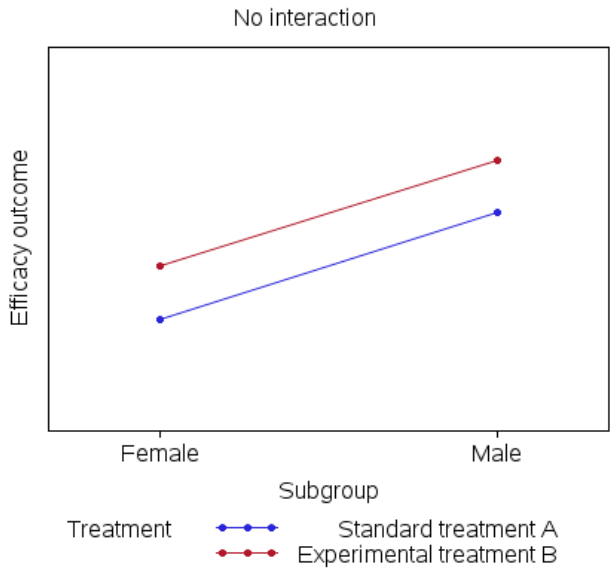
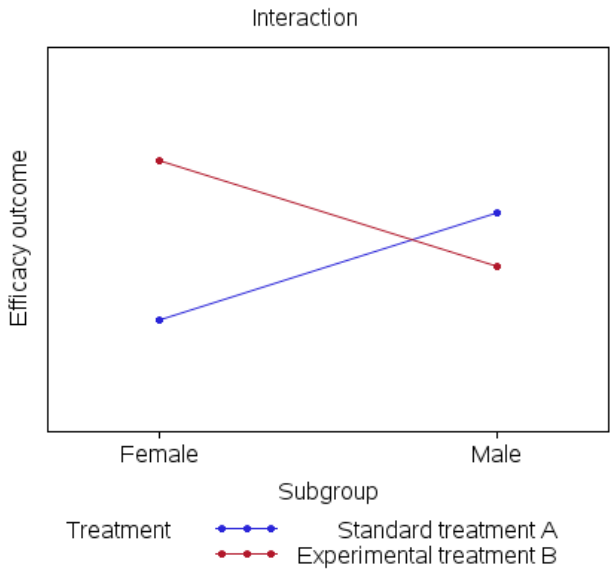
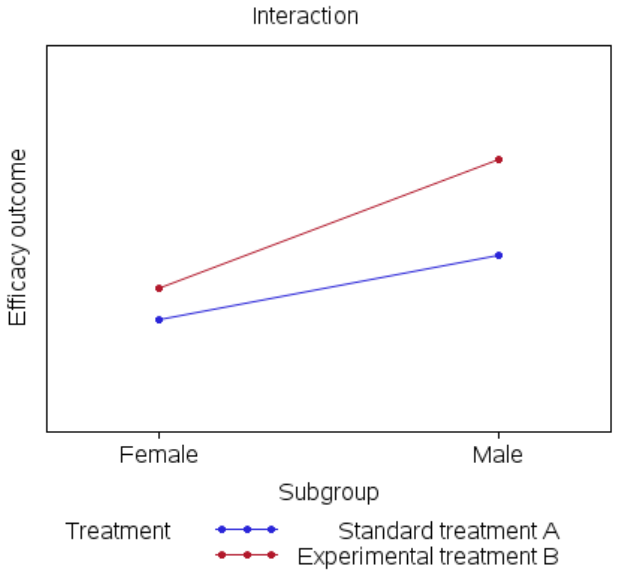
Example: Subgroup Analysis

Interaction test

- Interaction test: to check for an interaction between subgroup and treatment, i.e. if the treatment effect in one subgroup category is different to the treatment effect in the other subgroup category







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Example: Subgroup Analysis

Overall survival in female and male patients

	Female		Male	
	Experimental treatment B	**Standard treatment A**	**Experimental treatment B**	**Standard treatment A**
Number of patients, n (%)	29 (100)	28 (100)	71 (100)	72 (100)
Overall survival				
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Hazard ratio* (95% CI)	0.64 (0.36, 1.13)		0.51 (0.36, 0.73)	
Interaction p-value*	0.3612			

* from Cox proportional hazard regression model

- No significant interaction, therefore consistent benefit of experimental treatment B regardless of sex of the patient

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Example: Subgroup Analysis

Overall survival in female and male patients

	Female		Male	
	Experimental treatment B	**Standard treatment A**	**Experimental treatment B**	**Standard treatment A**
Number of patients, n (%)	29 (100)	28 (100)	71 (100)	72 (100)
Overall survival				
Number of patients with events, n (%)	25 (86.2)	26 (92.9)	62 (87.3)	68 (94.4)
Hazard ratio* (95% CI)	0.64 (0.36, 1.13)		0.51 (0.36, 0.73)	
Interaction p-value*	0.3612			

* from Cox proportional hazard regression model

- No significant interaction, therefore consistent benefit of experimental treatment B regardless of sex

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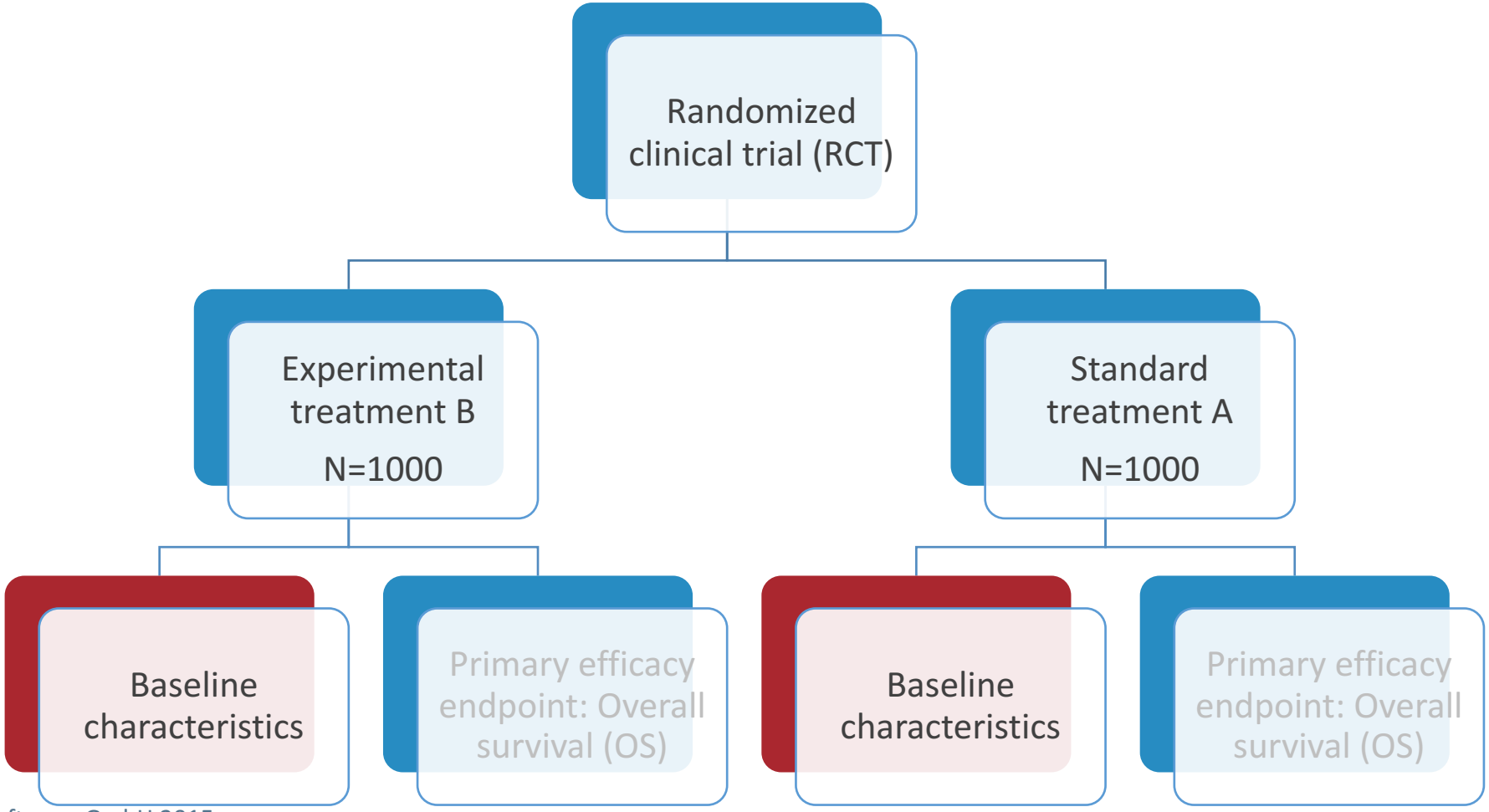
Example: Comparability of Baseline Characteristics

Baseline characteristics



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Example: Comparability of Baseline Characteristics

Calculating p-values for treatment comparison

- Often requested by journals
- Reviewer performed a Chi-square test, which resulted in significant p-value for a baseline variable
- Reviewer's conclusion: imbalance favored treatment A

- *Is this reasonable?*

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Example: Comparability of Baseline Characteristics

Calculating p-values for treatment comparison

- If in a *randomized* trial the p-value is:

significant

- Just by chance
- Randomization went wrong

not significant

- you cannot conclude that the baseline variable did not affect the result of the primary endpoint
- Randomization has worked

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Example: Comparability of Baseline Characteristics

Calculating p-values for subgroup comparison

- Requested by a journal for a subgroup analysis: are baseline characteristics balanced between subgroup categories?
- Reviewer's assumption: selection of explanatory variables for a multivariable model was based on imbalances at baseline
- Imbalances in baseline variables are possible between subgroups
  - baseline characteristics are randomized, i.e. balance between treatments but not necessarily between subgroup categories (e.g. older patients have normally more concomitant diseases)
- *Is this reasonable? → NO!*

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Example: Comparability of Baseline Characteristics

Calculating p-values for subgroup comparison

- If the p-value is:

significant

- Baseline variable is not balanced between subgroup categories
- Does not say that the baseline variable is related to the outcome

not significant

- Baseline variable is balanced between subgroup categories
- Does not say that the baseline variable is not related to the outcome

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Example: Comparability of Baseline Characteristics

Covariate correlation vs. covariate imbalance

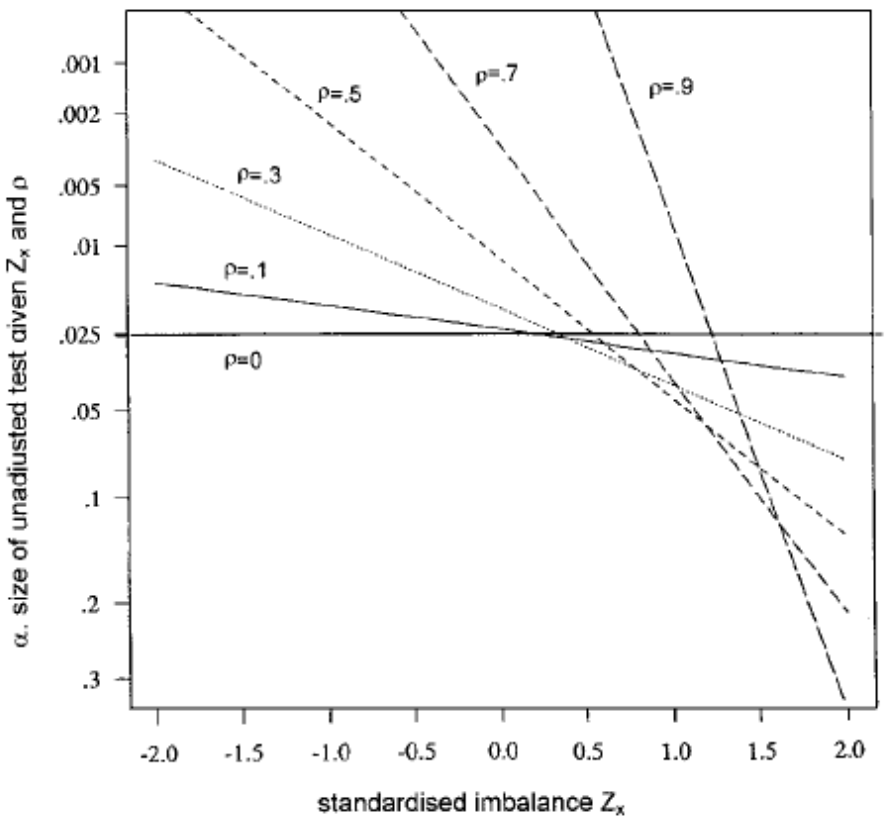

Figure 2. The effect of standardized covariate imbalance Z_x and the covariate's correlation with outcome ρ on the conditional size of unadjusted one-sided test (true $\alpha = 0.025$).

- From Pocock, S.J., Assmann, S.E., Enos, L.E. et al. (2002) Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems, Stat Med, 21, pp. 2917-2930

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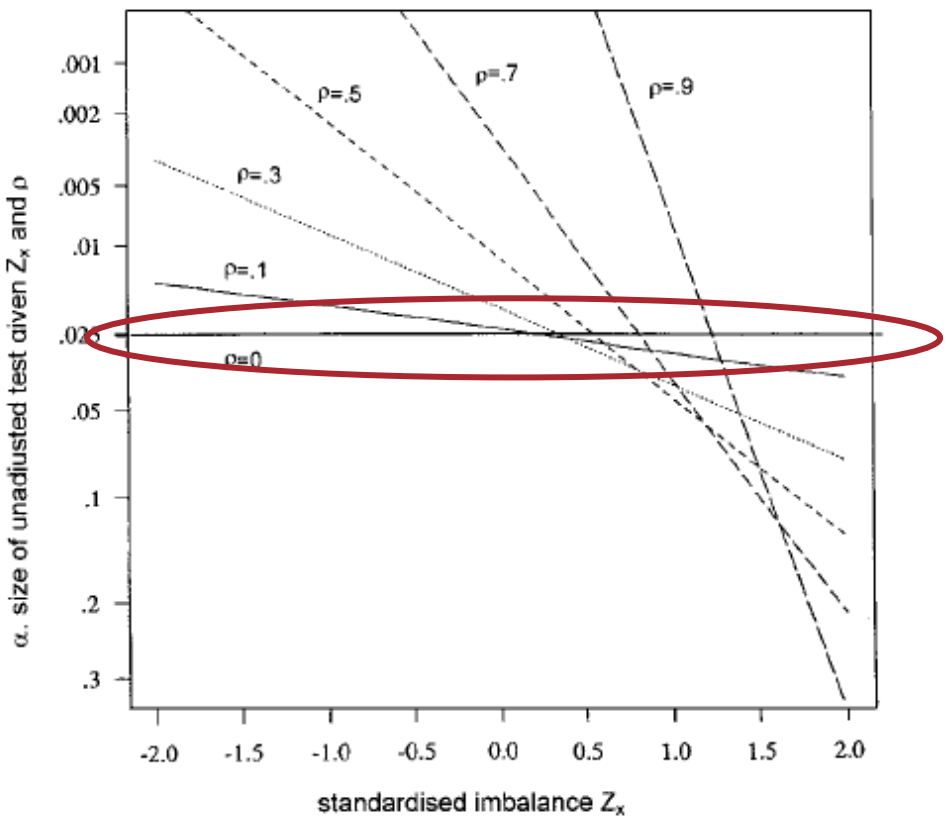

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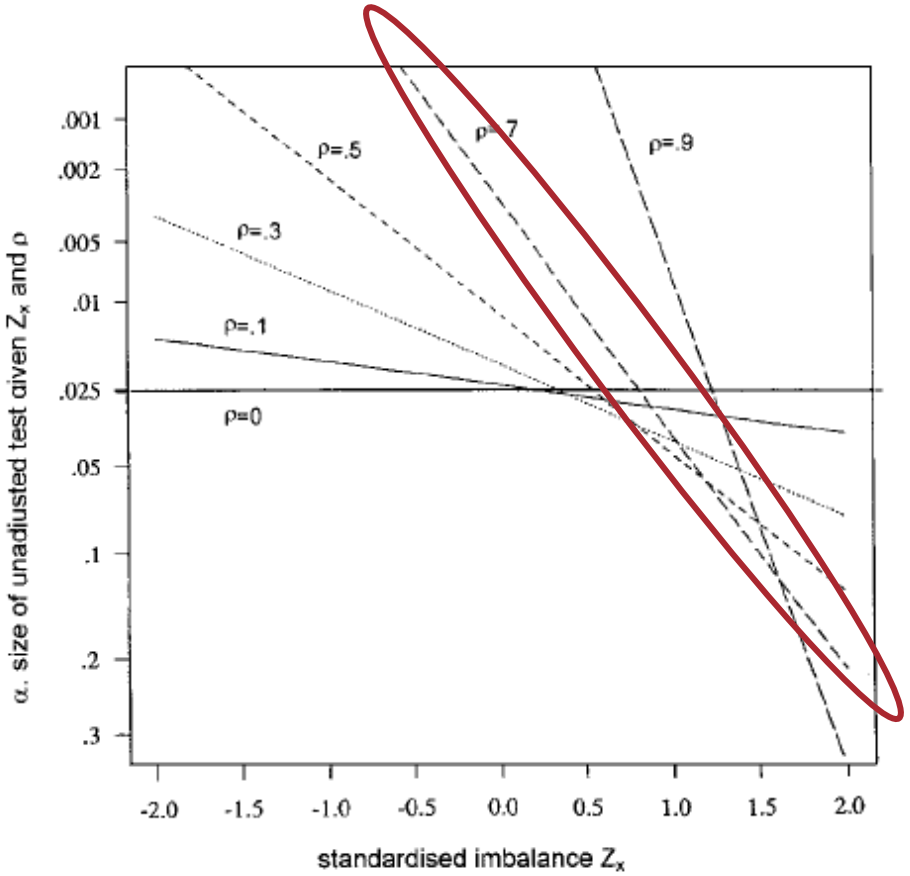
Example: Comparability of Baseline Characteristics

Covariate correlation vs. covariate imbalance



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Example: Comparability of Baseline Characteristics

Calculating p-values for treatment comparison

Does not make sense in a randomized trial

Tests whether the treatment groups have been randomly assigned

In case of balance between the groups no conclusion possible that baseline variable has no impact on the result of the (primary) endpoint

In case of imbalance between the groups no conclusion possible whether the baseline variable may have an impact on the result of the (primary) endpoint

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Summary

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Please…

- Don’t believe everything you see
- Check for handling of missing values
- Check if data is appropriately visualized
- Check if all data is included
- Check sample size (relevance of differences)
- Do an interaction test when performing subgroup analyses
- Use words like “reasonable”, “considerable”, “relevant” instead of “significant” in case of exploratory p-values
- Use p-values sparingly – look at confidence intervals instead

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Conclusion

Data visualization and new analytical tools

Does this mean:

- Efficient = less CPU usage
- Fast = takes few seconds to create e.g. a plot
- Interactive = tool immediately responds to the user's input
- Smart = knows what to do
- Friendly = nice user-interface
- Secure = validated tool
- Powerful = can do "everything"
- Fresh = delivers results without delay
- Easy = everybody can use it

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Conclusion

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Conclusion

Data visualization and new analytical tools

What is still necessary:

- Validation of results
- Validation of underlying dataset
- (Statistical) output review
- Analysis plan: select appropriate statistical methods

→ Raise people's awareness of these essential facts

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References

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THANK YOU!

Any questions?

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Back-up Slides

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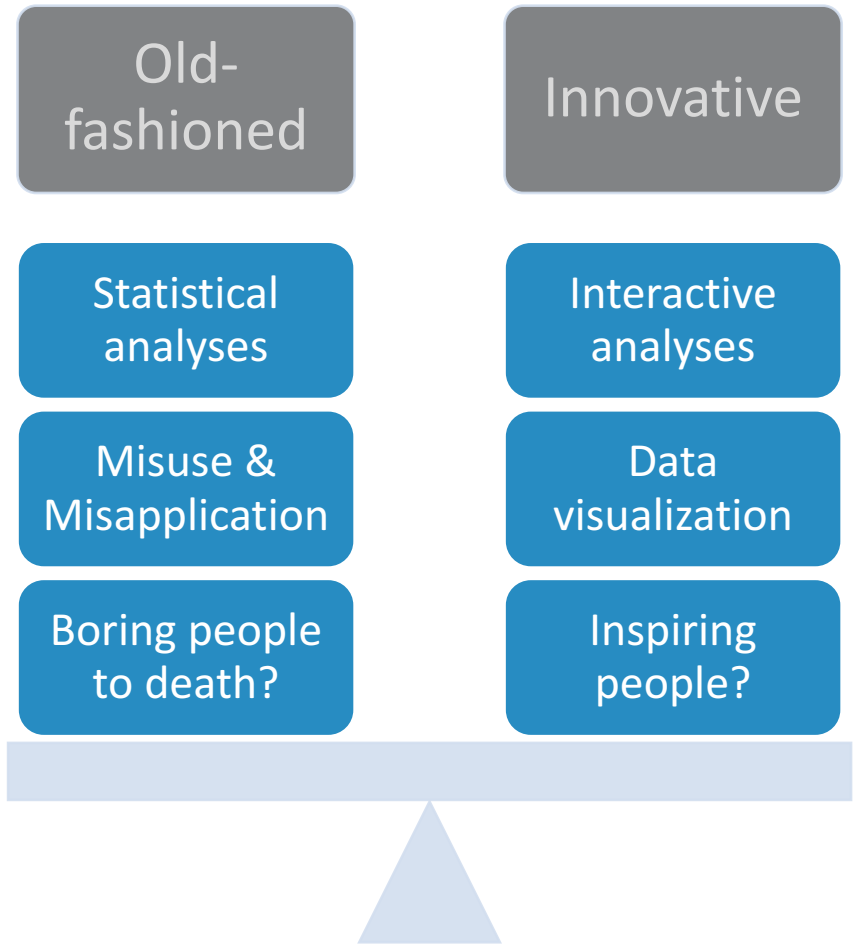
Introduction

Question: Old-fashioned vs. Innovative?



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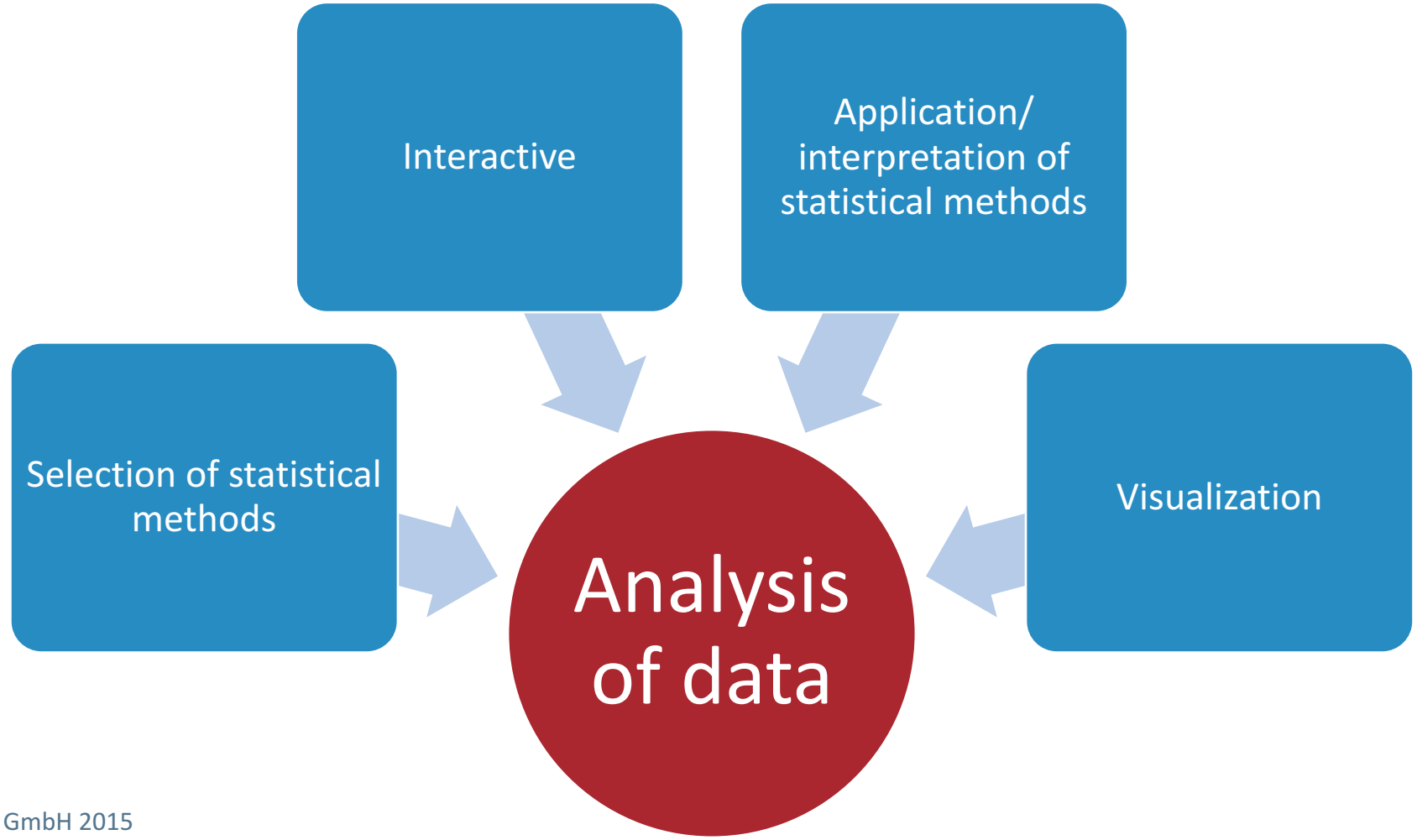
Introduction

Answer: NO!



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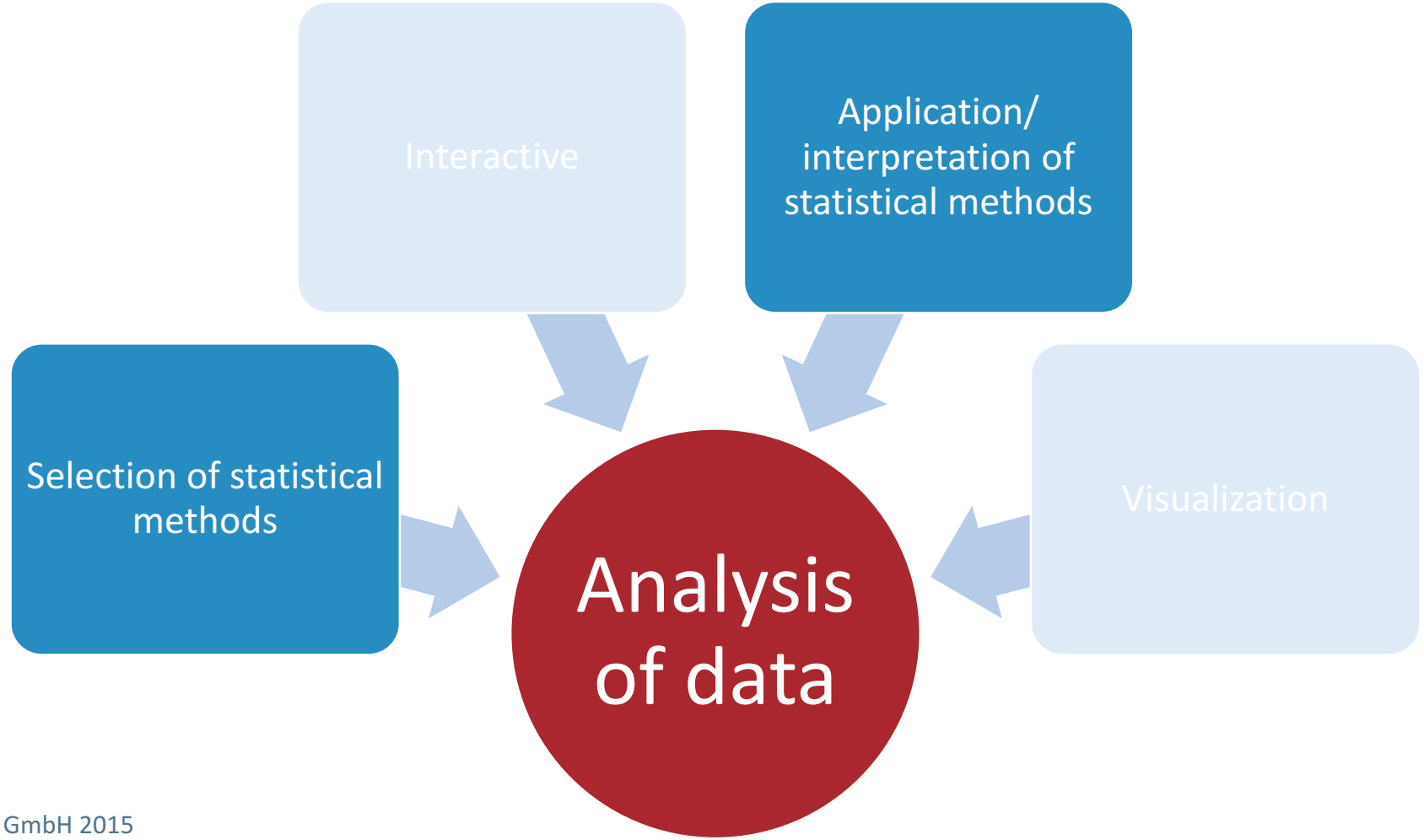
Introduction

Focus of this presentation



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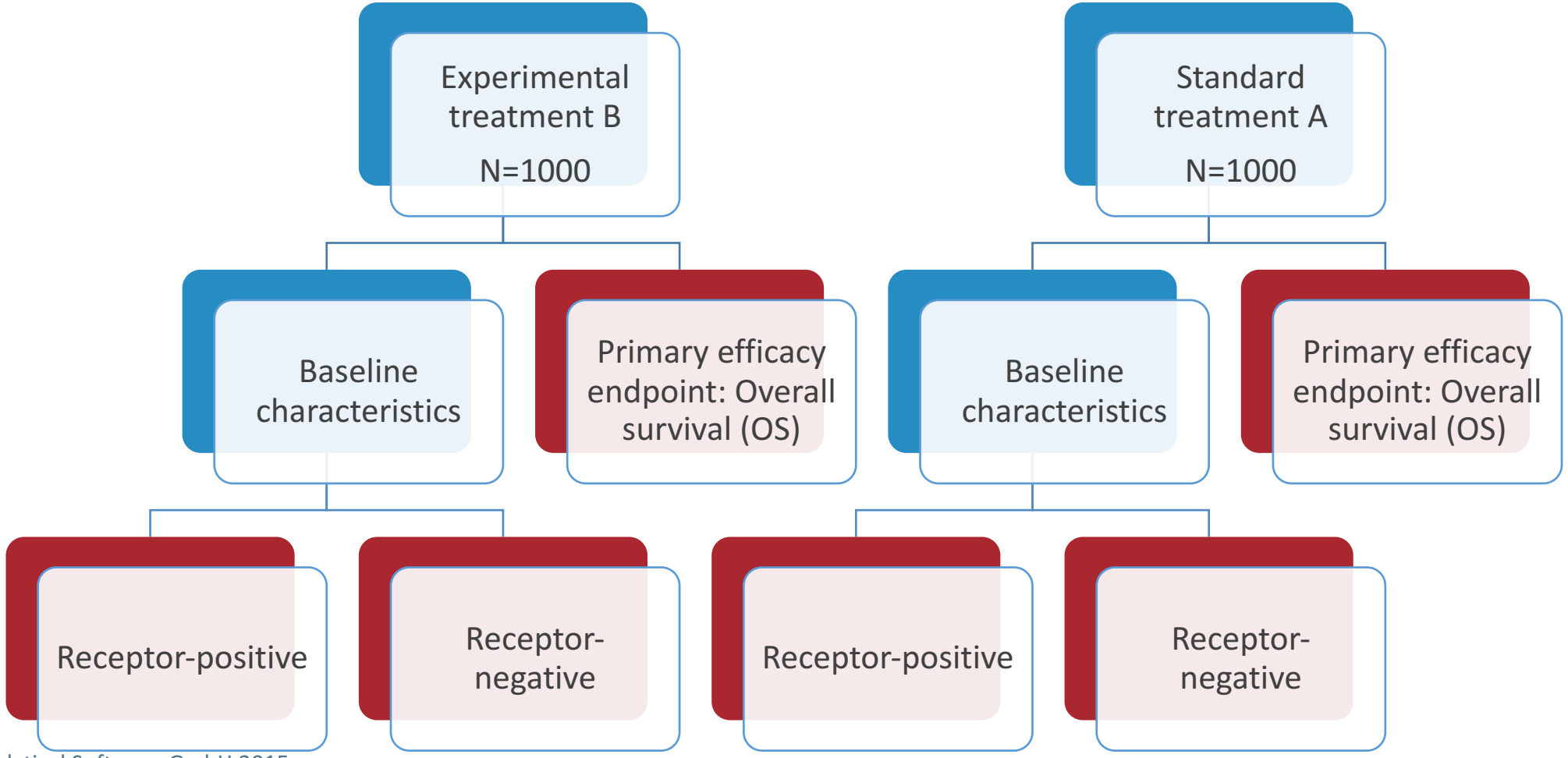
Example: Subgroup Analysis

Overall survival in receptor-positive and receptor-negative patients



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Example: Subgroup Analysis

Main results in overall population

	Experimental treatment B	Standard treatment A
Number of patients, n (%)	100 (100)	100 (100)
Overall survival		
Number of patients with events, n (%)	87 (87.0)	94 (94.0)
Hazard ratio* (95% CI)	0.85 (0.63, 1.14)	
p-value*	0.2692	

* from Cox proportional hazard regression model

- No significant benefit of experimental treatment B over standard treatment A
- Any benefit in specific subgroups?

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Example: Subgroup Analysis

Overall survival in receptor-positive and receptor-negative patients

	Receptor-negative		Receptor-positive	
	Experimental treatment B	**Standard treatment A**	**Experimental treatment B**	**Standard treatment A**
Number of patients, n (%)	68 (100)	66 (100)	32 (100)	34 (100)
Overall survival				
Number of patients with events, n (%)	63 (92.6)	61 (92.4)	24 (75.0)	33 (97.1)
Hazard ratio* (95% CI)	1.11 (0.78, 1.59)		0.41 (0.23, 0.72)	
Interaction p-value*	0.0057			

* from Cox proportional hazard regression model

- Significant interaction, only receptor-positive patients seem to benefit from the experimental treatment → however, limitations of subgroup analyses are still valid!

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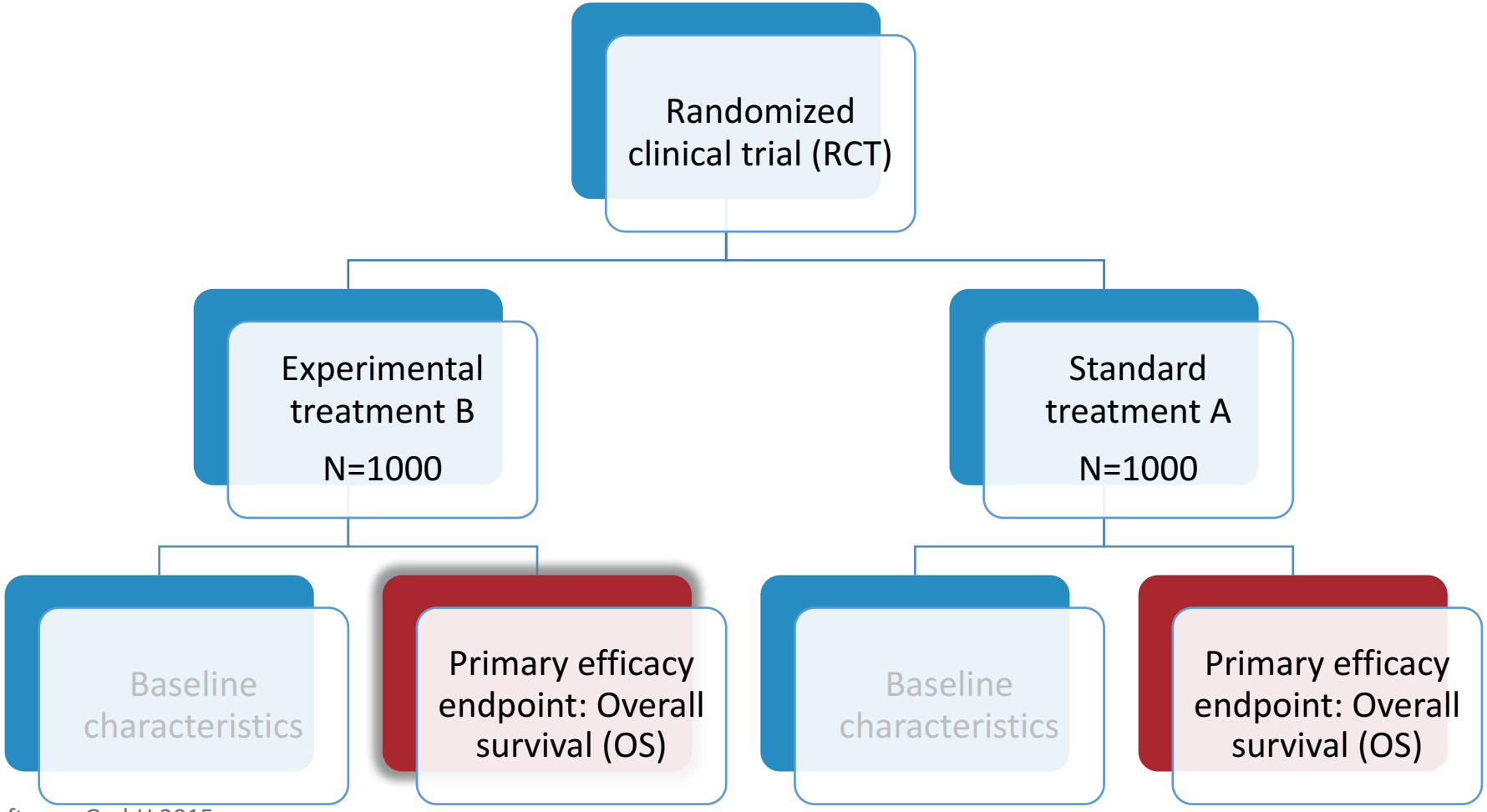
Next Simple Example

Primary endpoint



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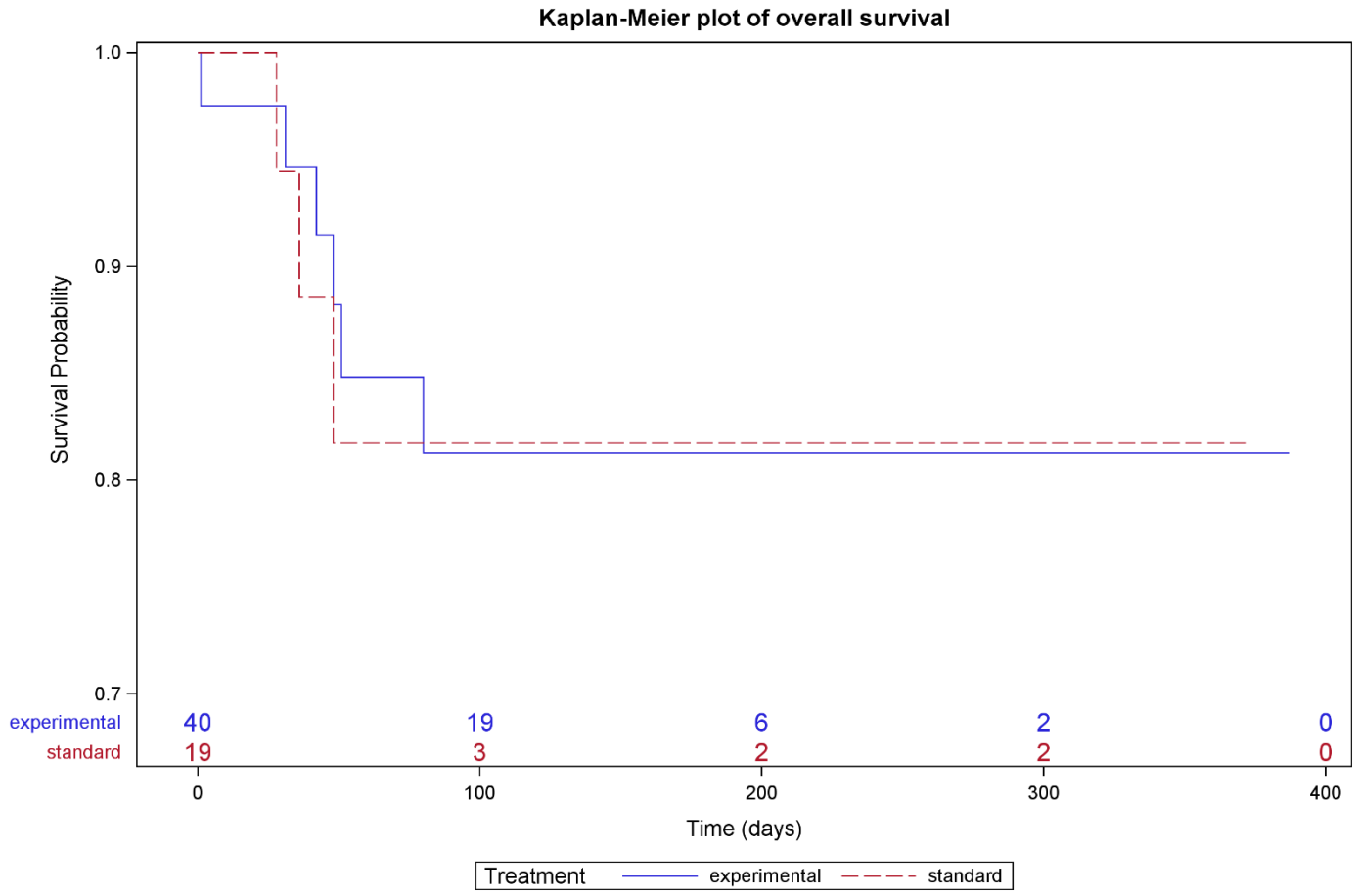
Next Simple Example

Kaplan-Meier Plot: Overemphasizing small difference



- y-axis only from 0.7 to 1.0
- Small difference appears more relevant than it actually is
- You cannot compare with other KM-plots

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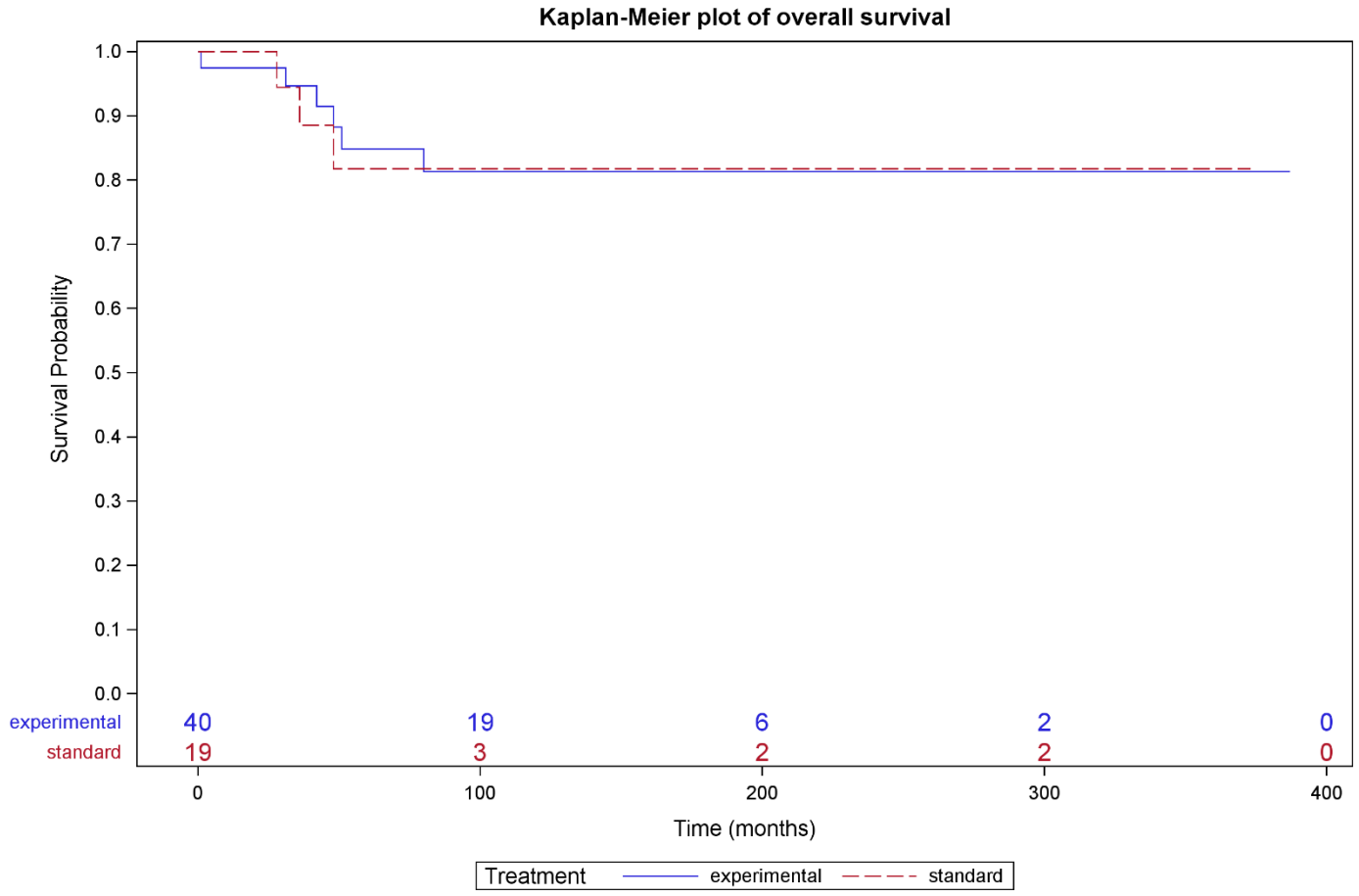
Next Simple Example

Kaplan-Meier Plot: Correct plot



- y-axis should always go from 0 to 1
- Similarly, for all plots showing percentage/probability on the y-axis
- Sometimes hard to read if data lies only in a small range of the y-axis

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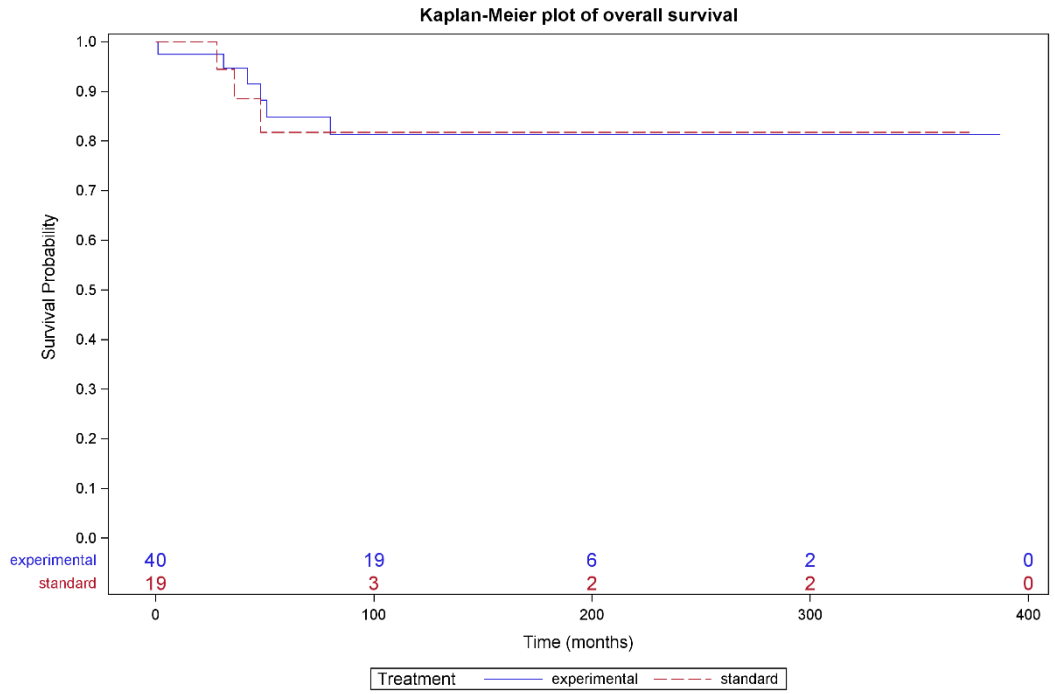
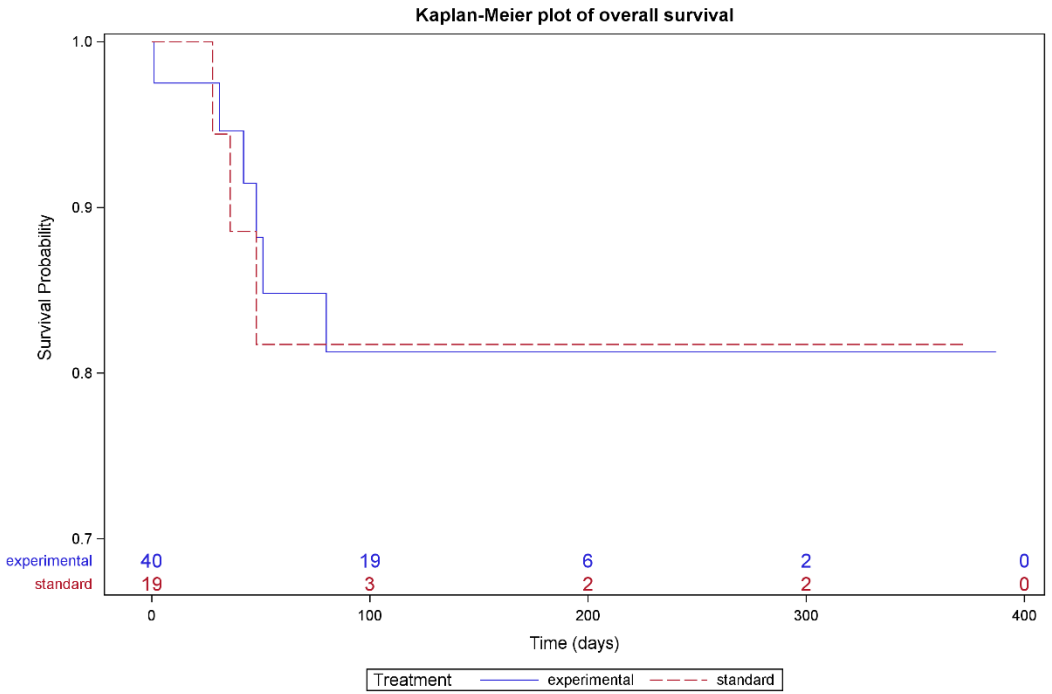
Next Simple Example

Kaplan-Meier Plot: Good compromise





- Show both if it is important to show the small difference

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